Remarks

There are no amendments to the claims. However, for ease of reference a complete listing of the claims follows the signature page of this response.

I. Addressing The Examiner's Rejections

A. Rejection of Claims 87, 88, 90-96, 98-108 and 114 Under 35 U.S.C. §103(a)

The Examiner rejected claims 87, 88, 90-96, 98-108 and 114 under 35 U.S.C. §103(a) asserting that the claims are unpatentable over Goeddel, et al., US 5,120,832, in view of Parker, et al., WO 00/40273, and Albrecht, et al., US 6,172,046, and further in view of Theeuwes, et al., US 4,976,966.

(1) The References Do Not Teach All of the Elements of the Claimed Invention.

To reject a claim based on combining prior art elements according to known methods to yield predictable results, the Examiner must resolve the Graham factual inquiries. *See Graham v. John Deere Co.*, 383 U.S. 1, 86 S. Ct. 684, 15 L Ed2d 545, 148 USPQ 459 (U.S. 1966). The Examiner must then articulate the following: (1) a finding that the prior art includes each element claimed with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference; (2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods and that in combination each element merely would have performed the same function as it did separately; (3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and (4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. (*See* Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* 57526, 57529 Federal Register / Vol. 72, No. 195.)

The cited references do not teach all of the elements of the independent claims as presented in the accompanying claim set. Accordingly, a case of *prima facie* obviousness has not been established.

First, none of the cited references teaches a method of treating Hepatitis C Virus (HCV) infection in a subject comprising administering a therapeutically effective amount of

omega interferon protein to the subject (*see* independent claims 87, 88 and 114). The reference of Goeddel, et al., teaches omega interferon; however, as noted by the Examiner "Goeddel *et al* does not specifically teach administration of omega IFN for treatment of HCV infection" (Office action, mailed 3 February 2009, page 4).

The reference of Parker, et al., teaches only the administration of a polynucleotide encoding an omega interferon (*see, e.g.,* Parker, et al., page 3, lines 2-4, lines 26-27, and page 5, lines 11-13). The Examiner asserted "the disclosure of Parker *et al,* by teaching that HCV infection can be treated by omega IFN expressed in a subject by administration of a polynucleotide encoding omega IFN, provides the motivation to treat HCV by administration of omega IFN protein" (*see* Office action, mailed 3 February 2009, page 5). This assertion is no more than a conclusionary statement for which the Examiner provides no supporting evidence. Essentially, the Examiner is equating treatment by administration of a protein to treatment using gene therapy. These two treatment methods are very different and the Examiner has not presented any evidence to support that there would be a reasonable expectation of success when extrapolating from one treatment method (gene therapy) to a completely different treatment method (direct administration of protein).

In the Declaration Under 37 C.F.R. §1.132, submitted 27 October 2008, Thomas R. Alessi, Ph.D. discusses limitations on the use of gene therapy for treatment of disease states. As the reference of the American Society of Gene Therapy (cited in the Declaration) clearly illustrates, gene therapy as of 2005 (about six years after the publication of the reference of Parker, et al.) was still in its infancy. Even to date, there have been few clinical advances in application of gene therapy methods. As stated in the Declaration:

> Accordingly, the Examiner's statement that "the polynucleotide of Parker would be expected to be expressed and translated into a therapeutically effective amount of IFN-ω, and this dose of IFN-ω would be expected to fall within the claimed dose ranges" (*see* Office action, mailed 28 May 2008, page 5) is completely unsubstantiated by the reference of Parker, et al. The Examiner has not provided any prior art supported evidence teaching predictable, sustained levels of protein expression in an animal subject using polynucleotide constructs. In fact, the Examiner's assertion of predictability appears to be contrary to the general state of the art of gene therapy as late as 2005, which is about six years after the publication of the reference of Parker, et al. (Declaration Under 37 C.F.R. §1.132, paragraph #10, submitted 27 October 2008.)

Further, the reference of Parker, et al., presents no data that demonstrate the usefulness of the administration of a polynucleotide encoding omega interferon for the treatment of HCV. The Examiner asserted the following:

> The reference demonstrates that administration of an omega IFN-expressing polynucleotide is capable of increasing serum omega IFN levels in a subject, and that this increased serum omega IFN can be beneficial in the treatment of HCV. (Office action, 3 February 2009, page 4.)

This assertion by the Examiner is an overstatement of the teachings of the Parker, et al., reference. The reference presents data showing, in mice and rats, that serum levels of omega interferon increase following injection of a vector construct encoding omega interferon (Examples 4 and 5; Parker, et al.). However, there is no data that shows that the increase in omega interferon provides any benefit for the treatment of HCV. The only evaluation of omega interferon's antiviral activity was performed *in vitro* against murine encephalomyocarditis virus (EMCV) (Example 3; Parker, et al.). EMCV is a picornavirus belonging to the family *Picornaviridae* whereas HCV is the only known member of the *hepacivirus* genus in the family *Flaviviridae*. Example 6 of Parker, et al., "Treatment Regimen with IFNω Plasmid DNA for Patients with Chronic Hepatitis B or C" is a prophetic example written in the present tense. The only virus shown by the reference to be affected by omega interferon is EMCV and only *in vitro* experimental data are given. No data related to *in vivo* treatment of any virus by administration of a polynucleotide encoding omega interferon to any animal is taught by the reference.

In the Declaration Under 37 C.F.R. §1.132, submitted 27 October 2008, Thomas R. Alessi, Ph.D. discusses the fact that the Examiner has presented no scientific basis to support an extrapolation from the teachings of the reference of Parker, et al., concerning *in vitro* inhibition of EMCV to *in vivo* treatment of HCV in subjects as is claimed in the present application. Administration of pegylated alpha interferon protein combined with ribavirin is the current standard of care for HCV. Treatment of HCV using alpha interferon protein was approved by the FDA in 1991, however, even alpha interferon has not been used and approved as a polynucleotide expression based treatment of HCV nearly 20 years later. As stated in the Declaration:

> Accordingly, even though the reference asserts an ability to treat HCV using a polynucleotide vector encoding omega interferon, the reference does not provide an enabling disclosure in this regard. I am not aware of any U.S. Food and Drug Administration (FDA) approved polynucleotide expression based treatment methods where the polynucleotide encodes alpha interferon. Further, I am not aware of any on-going clinical trials with such treatment. Treatment of chronic HCV infection with pegylated alpha interferon protein plus ribavirin is the current standard of care. (Declaration Under 37 C.F.R. §1.132, paragraph #9, submitted 27 October 2008.)

The reference of Albrecht, et al., also does not teach a method of treating HCV in a subject comprising administering a therapeutically effective amount of omega interferon protein to the subject. This reference teaches only the use of alpha interferon for the treatment of HCV. In the Office action, mailed 3 February 2009, the Examiner asserted the following:

> Further, the dosages and the frequency to be administered for the treatment of HCV is suggested by Albercht [*sic*] *et al.* While it is true that the references teach the administration of alpha IFN for the treatment HCV, the references also contemplate the use of omega IFN for the treatment of HCV. (Office action, 3 February 2009, page 8.)

Contrary to the Examiner's assertion, the reference of Albrecht, et al., does not contemplate the use of any interferon other than alpha interferon for the treatment of HCV (*see* Albrecht, et al., col. 3, line 53, to col. 4, line 12). The reference is directed to a method for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by use of a combination therapy using a therapeutically effective amount of ribavirin and a therapeutically effective amount of interferon-alpha for a time period of from 20 up to 80 weeks (*see* Albrecht, et al., Abstract). The Examiner has presented no evidence or reasoning why there would be a reasonable expectation of success to extrapolate dosages related to the use of one beneficial agent (alpha interferon) to a different beneficial agent (omega interferon); particularly in view of the Declaration of Dr. Alessi which states "[t]he Examiner is making the assumption that interferons are interchangeable in their pharmaceutical activities. This assertion is unsupported by the Examiner and is inconsistent with what is known regarding omega interferon." (Declaration Under 37 C.F.R. §1.132, paragraph #11, submitted 27 October 2008.)

Further, the reference of Theeuwes, et al., does not teach a method of treating HCV in a subject comprising administering a therapeutically effective amount of omega interferon protein to the subject. The reference is directed to osmotically driven pumps for administering a drug in fluid form.

Second, none of the cited references teaches or suggests the administration at the claimed microgram per week dosage ranges of omega interferon protein. The reference of Parker, et al., teaches only the administration of constructs comprising polynucleotides encoding omega interferon. It is notoriously difficult in the field of gene therapy to control and maintain a predetermined range of expressed polypeptide over time from constructs comprising polynucleotides encoding polypeptides (*see* Declaration Under 37 C.F.R. §1.132, paragraph #10, submitted 27 October 2008). Unpredictability associated with expression vectors, problems with innate immunity and tissue damage, problems with predictable gene expression and serious safety issues are generally recognized (*see, e.g.,* American Society of Gene Therapy, "Challenges in Advancing the Field of Gene Therapy: A Critical Review of the Science, Medicine, and Regulation," discussed in the Declaration Under 37 C.F.R. §1.132, paragraph #10, submitted 27 October 2008, and attached as Appendix B to the declaration) as limiting the clinical success of gene therapy methods such as those disclosed by the reference of Parker, et al.

The Examiner asserted the following:

> In the instant case, the general conditions of the claims, administration of omega IFN for treatment of HCV infection, are obvious in view of the combination of Goeddel *et al*, Parker *et al*, Albercht [*sic*] *et al*, and Theeuwes *et al*, and therefore it would be obvious to optimize conditions such as dosage and timing and route of administration. (Office action, mailed 3 February 2009, page 6.)

However, as discussed above "the general conditions of the invention" are not obvious in view of the prior art and the Examiner presents no evidence to support the assertion that the claimed ranges are nothing more than "routine optimization" particularly in view of the fact that no reference teaches treatment of HCV by direct administration of omega interferon protein.

Further, HCV has been recalcitrant to treatment and even using the currently FDA-

approved standard of care, pegylated alpha interferon with ribavirin, patients having chronic HCV infection resistant to the treatment method are common (*see, e.g.,* the present specification, ¶0007; *see* also, Buckwold, et al., page 118, cols. 1-2; for a copy of Buckwold, et al., *see* Declaration Under 37 C.F.R. §1.132, Appendix D, submitted 27 October 2008). As demonstrated in the present application, subjects having chronic HCV infection and even subjects having chronic HCV infection resistant to treatment with alpha interferon (with or without ribavirin) show clearance of HCV in response to the treatment methods of the present invention (*see, e.g.,* specification, ¶0058-¶0059).

The Examiner has not presented any evidence to support the assertion that one of ordinary skill in the art would predict that omega interferon is able to treat HCV infection in a subject in need of such treatment.

In the Declaration Under 37 C.F.R. §1.132, Thomas R. Alessi, Ph.D. (submitted 27 October 2008) discusses the limitations of the teachings of the reference of Goeddel, et al., including the Examiner's incorrect assumption that interferons are interchangeable in their pharmaceutical activities. In the Office action, mailed 3 February 2009, the Examiner asserted the following:

> Specifically, Goeddel *et al*, by teaching that omega IFN protein possesses type I IFN biological activity, including antiviral activity, provides motivation to use omega IFN, and also provides the skilled artisan with the knowledge of a specific omega IFN polypeptide. (Office action, mailed 3 February 2009, page 5).

This assertion is unsupported by the Examiner and is inconsistent with what is known regarding omega interferon and interferons in general (*see* Declaration Under 37 C.F.R. §1.132, paragraph #11, submitted 27 October 2008). In the Declaration, Dr. Alessi discusses the very different physical and *in vitro* properties of omega interferon relative to alpha interferon (*See* Declaration Under 37 C.F.R. §1.132, paragraph #12, submitted 27 October 2008). Dr. Alessi also discusses the reference of Viscomi (Appendix C of the Declaration) that teaches that omega interferon and alpha interferon show distinct properties and significant variety in their biological actions (*see* Declaration Under 37 C.F.R. §1.132, paragraph #13, submitted 27 October 2008). Further, the reference of Buckwold, et al., points out several distinct differences between the antiviral activities of alpha, beta, gamma,

and omega interferons (*see* Declaration Under 37 C.F.R. §1.132, paragraph #13, submitted 27 October 2008). Thus, the Examiner's assertions regarding expectations of omega interferon to predictably perform the same as alpha interferon are merely conclusionary and not substantiated by any evidence, on the contrary the evidence presented herein contradicts the Examiner's assertions.

The dependent claims distinguish over the combination of references by virtue of their incorporation of the limitations of the independent claim from which they depend.

Accordingly, the cited references do not meet the first three prongs of the four pronged factual inquiries required for a determination of obviousness. (The fourth prong, i.e., secondary considerations, is discussed below in "(3) Secondary Considerations.") First, the Examiner has not presented a finding that the prior art includes each element claimed with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference. In the present case, the cited references do not teach a method of treating HCV in a subject comprising administering a therapeutically effective amount of omega interferon protein to the subject nor do the cited references teach using the claimed dosage ranges. Second, the Examiner has failed to provide a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods and that in combination each element merely would have performed the same function as it did separately. In particular, the Examiner has not presented any evidence to support that a protein expressed *in vivo* from a vector, that is, administered via a gene therapy method, would perform the same function as a directly administered protein given at particular dosing levels. Further, the Examiner has not presented any evidence to support that omega interferon would predictably perform the same as alpha interferon for the majority of treatment methods. Finally, the Examiner has not provided a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable. In fact, the Declaration Under 37 C.F.R. §1.132 of Dr. Alessi, submitted 27 October 2008, explicitly sets forth numerous reasons that one of ordinary skill in the art would not have recognized that the results of the combination were predictable.

Applicant submits that the Examiner has failed to establish a case of *prima facie*

obviousness for the presently claimed invention in view of the above-presented arguments. Applicant respectfully requests that the rejection under 35 U.S.C. §103 be withdrawn.

(2) The Parker, et al., Reference Teaches Away From the Claimed Invention.

Even if, for the sake of argument, the elements of the invention are taught by the prior art, which Applicant maintains they are not, obviousness cannot be established if the prior art teaches away from the claimed invention. The Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* (57526, at 57529 Federal Register / Vol. 72, No. 195) state the following:

> Note that combining known prior art elements is not sufficient to render the claimed invention obvious if the results would not have been predictable to one of ordinary skill in the art. (Regarding "teaching away" the guidelines cite, *United States v. Adams*, 383 U.S. 39, 51–52, 148 USPQ 479, 483 (1966), wherein the Supreme Court would not require that one of ordinary skill in the art ignore the teaching away of the prior art.)

As discussed herein above, the reference of Parker, et al., teaches only the administration of a polynucleotide encoding an omega interferon (*see, e.g.,* Parker, et al., page 3, lines 2-4, lines 26-27, and page 5, lines 11-13). In fact, the reference of Parker, et al., notes that "IFN-omega has never been used for the treatment of infectious diseases, even in the form of a recombinant protein" (Parker, et al., page 2, lines 11-12; emphasis added). Further, the reference of Parker, et al., states "[T]reatment of infectious diseases with an interferon (IFN) has traditionally involved repeat injections of large doses of recombinant protein" (Parker, et al., page 1, lines 10-11). The reference goes on to state "[C]learly, there is a need for an improved delivery system for treating infectious diseases with IFNs." Following this introduction, all of the teachings of the reference of Parker, et al., are directed to the treatment of infectious disease by administering a polynucleotide construct into a tissue of a mammal and the advantages thereof. The reference does not teach a method involving administration of omega interferon protein nor any advantage to such a method.

A reference should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered. *See, e.g., Bausch & Lomb v. Barnes-*

Hind/Hydrocurve, 796 F.2d 443, 230 USPQ 416 (Fed. Cir. 1986). Prior art may be considered not to teach an invention, and thereby fail to support an obviousness rejection, when the stated objectives of the prior art reinforce such an interpretation. *See, e.g., WMS Gaming Inc. v. International Game Tech*, 184 F.3d 1339, 51 USPQ2d 1385, 1400 (Fed. Cir. 1999). The stated objective of the reference of Parker, et al., is to provide an improved delivery system for treating infectious diseases with interferons wherein the system is the delivery of polynucleotides encoding omega interferon. Accordingly, the reference of Parker, et al., teaches away from the methods of the present invention that use administration of a therapeutically effective amount of omega interferon protein to a subject. Applicant submits that the Examiner's modification of the reference of Parker, et al., to achieve a contrary purpose to the stated objective of the reference is inappropriate and does not support a conclusion of obviousness. None of the other cited references makes up for this shortcoming of the reference of Parker, et al.

The Examiner asserted the following relying on the holding of *In re Keller*:

> Applicant appears to be arguing the references individually. The Office relied on the combined teaching to show the obviousness of the instant invention. It is noted that the courts have held that it is not necessary that the claimed invention be expressly suggested in anyone or all of the references to justify combining their teachings; rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art, *In re Keller*, 642 F.2d 413, 288 USPQ 871 9ccpa [*sic*] 1981).

The holding in *In re Keller* was as follows: "The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference.... Rather, the test is what the combined teachings of those references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). However, the fact pattern in *In re Keller* is very different from the fact pattern in the present application.

In *In re Keller,* both of the cited references (Keller and Berkovits) disclosed heart stimulators that used R-C type timing circuits. The third reference (Walsh) taught the use of digital type timing circuits in place of R-C type timing circuits in conventional heart stimulators. The combination of elements was from one heart stimulator device into another heart stimulator device. But in the present application, unlike the fact pattern in *In re Keller*,

the claimed combination changes the principle of operation of the cited reference relative to the claimed invention. The reference of Parker, et al., is directed to an alternative and allegedly superior method of treatment using gene therapy delivery of omega interferon. The reference of Albrecht, et al., is directed to treatment of HCV using alpha interferon. As stated in the declaration it is not reasonable to assume that one could substitute, with a reasonable expectation of success, direct administration a given protein for a gene therapy method using a vector encoding the protein; further it is not reasonable to assume an expectation of success with the substitution of one interferon for another. The Examiner has not presented any evidence that it would be predictable to extrapolate teachings related to gene therapy methods to treatment methods using direct administration of protein. Accordingly, the Examiner's reliance on the holding of *In re Keller* is misguided.

The Examiner went on to assert that "[i]n addition, the motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07." (Office action, mailed 3 February 2009, page 7; emphasis in original.) However, as discussed above, the teachings of the Parker, et al., reference regarding gene therapy are presented as an alternative to, and asserted to be superior to, direct administration of a protein. Gene therapy methods are not interchangeable with treatment methods using direct administration of a protein. Thus, the two treatment methods do not have defined elements in common that would be expected to perform the same functions to achieve the same expected results wherein the same elements affect the success of each method. A proposed gene therapy treatment for HCV is not comparable to direct administration of omega interferon protein for the treatment of HCV and the Examiner has presented no evidence to identify what expected function achieves what expected result.

Finally, in the Office action, mailed 3 February 2009, the Examiner alleged the following:

> Contrary to Applicant's assertion that the Office is suggesting or teaching gene therapy protocols by the use of Parker et al., the Office relied on this reference to show that HCV can be treated by omega IFN administration. The reference also taught that serum omega IFN levels in a subject can be increased, and that this increased serum omega IFN can be beneficial in the treatment of HCV. While it is true that there is no in vivo data is presented by

> Parker *et al.*, there is no such requirement for data because the art often extrapolates the *in vitro* data. In addition, the Office is not FDA [*sic*] to require *in vivo* data. Contrary to Applicant's assertion that Parker *et al.* teaches away from the invention it dose [*sic*] teach the administration omega IFN for the treatment of HCV. (Office action, mailed 3 February 2009, page 8.)

First, the Parker, et al., reference does not teach administration of omega interferon protein for the treatment of HCV it only proposes a gene therapy method. Second, there are no data in the reference that demonstrated that the amount of omega interferon expressed after administration of a vector encoding omega interferon would benefit the treatment of HCV. Third, there is no *in vitro* data regarding treatment of HCV in the reference of Parker, et al.; thus there can be no "extrapolation" of *in vitro* data. Fourth, there is no data at all in the reference of Parker, et al., regarding any therapeutic effect of expressed levels of omega interferon against HCV. Fourth, the reference of Parker, et al., does not teach direct administration of omega interferon protein for the treatment of HCV but does teach treatment of infectious disease by administering a polynucleotide construct into a tissue of a mammal and the alleged advantages of a gene therapy approach.

Additionally, there is no enabling support in the reference of Parker, et al., to show that the treatment method proposed by Parker, et al., would be effective for in vivo treatment of HCV infection in subjects. The reference of Parker, et al., is a published PCT International Application that was never, to the best of Applicant's knowledge, examined by any recognized national examining office. Published PCT International Applications are not peer reviewed. Accordingly, there is no presumption of validity of any kind associated with the Parker, et al., reference, in particular the reference has not been critically evaluated regarding its scope of enablement.

The references do not teach or provide any evidence to support the Examiner's conclusions. Specifically, the Examiner has not demonstrated that any reasonable expectation of success is present when extrapolating teachings regarding gene therapy to treatment by direct administration of protein nor has the Examiner presented any evidence that one of ordinary skill in the art would have any reason to expect that one method would work based on results of the other method.

Accordingly, Applicant submits that the Examiner has failed to establish a case of

prima facie obviousness for the presently claimed invention as modification of the reference of Parker, et al., along the lines suggested by the Examiner is counter to the stated intention of the reference. In view of the above-presented arguments, Applicant respectfully requests that the rejection under 35 U.S.C. §103 be withdrawn. The dependent claims distinguish over the combination of references by virtue of their incorporation of the limitations of the independent claim from which they depend.

(3) Secondary Considerations

In *KSR Int'l Co. v. Teleflex Inc.,* 127 S. Ct. 1727; 167 L. Ed. 2d 705; 2007 U.S. LEXIS 4745; 75 U.S.L.W. 4289; 82 USPQ2D 1385 (U.S. 2007), the Supreme Court reaffirmed use of the Graham factors in the determination of obviousness under 35 U.S.C. §103(a). The four factual inquiries under Graham are: (a) determining the scope and contents of the prior art; (b) ascertaining the differences between the prior art and the claims in issue; (c) resolving the level of ordinary skill in the pertinent art; and (d) evaluating evidence of secondary consideration. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545, 148 USPQ 459, 467 (U.S. 1966).

The reference of Parker, et al., presents no data that demonstrate the effectiveness of the administration of a polynucleotide encoding omega interferon for the treatment of HCV. The single example related to treatment of HCV is a prophetic example. In addition, as noted above, the reference of Parker, et al., does not teach a method of treating HCV in a subject comprising administering a therapeutically effective amount of omega interferon protein to the subject. Applicant's specification teaches not only that administration of omega interferon protein is useful for the treatment of HCV infection (*see, e.g.,* specification ¶0059 and Figure 2) but also that administration of omega interferon protein is useful for the treatment of HCV infection in individual subjects with chronic HCV infection resistant to treatment with alpha interferon (with or without ribavirin). These advantages of the present invention were unrecognized in the prior art. In addition, as stated by the later published reference of Buckwold, et al., treatment of subjects with omega interferon protein is well tolerated (*see, e.g.,* Abstract and page 119, col. 1, first full paragraph). This presents another advantage of the treatment method of the present invention.

In the Office action the Examiner asserted "Applicant appears to claim unexpected results, there is no evidence provided for such" (Office action, mailed 3 February 2009, page 8). This statement is not true and Applicant has previously described the unexpected results arising from the practice of the present invention. These unexpected results are restated here.

First, as the reference of Buckwold, et al., noted "[O]ther antiviral therapies to treat HCV-infected patients are desperately needed" (page 118, col. 2). The present invention provides such antiviral therapy and the methods of treatment disclosed in the present specification are consistent with the teachings of the reference of Buckwold, et al., concerning the antiviral activity of omega interferon against HCV.

Second, in the Declaration Under 37 C.F.R. §1.132, submitted 27 October 2008, Dr. Alessi discusses that he was involved in working on the therapeutic applications of alpha interferon while at Schering-Plough Research Institute (*see* Declaration Under 37 C.F.R. §1.132, paragraph #3 and Appendix A), in particular treatment of HCV infection using interferon alfa-2b. Schering-Plough had the first FDA approved alpha interferon product for the treatment of HCV. Dr. Alessi points out that omega interferon has been known to one of ordinary skill in the art since the mid-1980's yet, prior to the work at Intarcia Therapeutics, Inc., omega interferon protein had not been used for the treatment of HCV infection (*see* Declaration Under 37 C.F.R. §1.132, paragraph #16).

Third, in the Declaration, Dr. Alessi discusses the actual clinical work that has been and continues to be conducted by Intarcia Therapeutics, Inc., proving the value and usefulness of treatment of HCV using omega interferon protein both by injection and by implantable osmotic delivery systems to deliver the protein continuously over extended time periods (*see* Declaration Under 37 C.F.R. §1.132, paragraph #15). The data demonstrate that treatment with omega interferon protein was well-tolerated by patients and demonstrate excellent anti-HCV activity. The poster (Declaration Under 37 C.F.R. §1.132, Appendix E, presented at Digestive Disease Week 2007 Meeting) also illustrates an ongoing clinical trial, sponsored by Intarcia Therapeutics, Inc., using an implantable osmotic delivery system (DUROS®; ALZA Corporation, Mountain View, CA) to deliver omega interferon protein continuously over extended time periods to patients who have failed the standard treatment of pegylated alpha interferon plus ribavirin. Current results from this clinical trial also

demonstrate that treatment of these patients (i.e., patients whose HCV infections exhibit primary or secondary resistance to treatment with alpha interferon) with omega interferon protein is well-tolerated by patients and provides excellent anti-HCV activity.

Accordingly, these unappreciated and unexpected advantages of the present invention should be evaluated in the context of any asserted rejection under 35 U.S.C. §103(a). Applicant submits that the Examiner has not addressed these secondary considerations and respectfully requests their consideration.

(4) Opinion of Dr. Alessi as one of ordinary skill in the art

Finally, in paragraph #17 of the Declaration, Dr. Alessi further provides his opinion as an expert in the field of interferons as antiviral agents that:

- in the absence of any prior *in vitro* data and in particular in the absence of clinical data on the usefulness of the administration of omega interferon protein for the treatment of HCV, any assertion of the probable efficacy of such treatment based on the cited references is no more than wishful thinking;
- the references cited by the Examiner do not support a finding that a typical scientist having ordinary skill in the art at the time the invention was made would have assumed that administration of omega interferon protein would be efficacious for the treatment of HCV based on the assertion of the Parker, et al., reference that a polynucleotide encoding omega interferon might be used to treat HCV;
- the references do not support a finding that a typical scientist having ordinary skill in the art at the time the invention was made would assume that omega interferon protein would be expected to perform all the same functions as alpha interferon;
- the references do not support a finding that a typical scientist having ordinary skill in the art at the time the invention was made would be motivated to administer omega interferon protein for the treatment of HCV rather than the standard of treatment of alpha interferon protein; and
- the references do not support a finding that a typical scientist having ordinary skill in the art at the time the invention was made would have recognized that the HCV treatment results obtained by the claimed methods were predictable.

As discussed herein above and in the Declaration, the Examiner has not provided evidence to support the Examiner's assertion that the presently claimed invention is obvious over the combination of Goeddel, et al., US 5,120,832, in view of Parker, et al., WO 00/40273, and Albrecht, et al., US 6,172,046, and further in view of Theeuwes, et al., US 4,976,966.

In view of the above-arguments and the Declaration Under 37 C.F.R. §1.132 by Dr. Alessi, Applicant submits that the Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, Applicant respectfully requests withdrawal of the rejection of the claims under 35 U.S.C. §103.

B. Rejection of Claims 86, 97, 103 and 109-113 Under 35 U.S.C. §103(a).

The Examiner rejected claims 86, 97, 103 and 109-113 under 35 U.S.C. §103(a) asserting that the claims are unpatentable over Goeddel, et al., US 5,120,832, in view of Parker, et al., WO 00/40273, and Albrecht, et al., US 6,172,046, and further in view of Theeuwes, et al., US 4,976,966, and Guillen, et al., US 6,074,673.

The combination of references, as discussed herein above, does not teach all of the elements of the claimed invention. The addition of the reference of Guillen, et al., to the references cited in the previous rejection does not make up for any of the shortcomings of the cited references as discussed herein above. The reference of Guillen, et al., does not teach omega interferon protein nor does it teach treatment of HCV. The reference mentions allergy-desensitization kits for use in desensitizing an allergy patient to one or more allergens.

In order for a combination of references to render obvious a claimed invention, all of the recited elements of claimed invention must be taught by the combination of references. Further, the combination of references does not render the presently claimed invention obvious because the primary reference teaches away from the present invention as discussed herein above. Accordingly, the Examiner has failed to establish a case of *prima facie* obviousness for independent claims 87, 88 and 114. The dependent claims distinguish over the combination of references by virtue of their incorporation of the limitations of the independent claim from which they depend.

Accordingly, Applicant submits that the Examiner has failed to establish a case of *prima facie* obviousness. In view of the above-presented arguments, Applicant respectfully requests that the rejections under 35 U.S.C. §103 be withdrawn.

C. Provisional Non-Statutory Obviousness-Type Double Patenting Rejections.

The Examiner provisionally rejected claims 87, 88, 90-96, 98-108 and 114 on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 65 and 86-104 of co-pending Application No. 10/982,532.

The Examiner provisionally rejected claims 87, 88, 90-96, 98-108 and 114 on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 1, 5-7, 17-22, 25 and 40-55 of co-pending Application No. 11/811,415.

As these are both provisional obviousness-type double patenting rejections and because no conflicting claims have been patented, Applicant respectfully requests that the provisional rejections be held in abeyance until agreement on allowable subject matter is established in the present application. Applicant notes that co-pending Application Nos. 10/982,532 and 11/811,415 are assigned to Intarcia Therapeutics, Inc., as is the present application.

II. Conclusion.

Applicant respectfully submits that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art.

Please direct all further communications in this application to:

CUSTOMER NUMBER: 000074866

Barbara G. McClung, Esq.
Vice President, General Counsel and Corporate Secretary
Intarcia Therapeutics, Inc.
24650 Industrial Blvd
Hayward CA 94545
Phone: (510) 782-7800 ext 122
Fax: (510) 782-7801

If the Examiner notes any further matters that the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned at (650) 780-9030.

Respectfully submitted,

Date: 3 February 2010 By: /Gary R. Fabian/
Gary R. Fabian, Ph.D.
Registration No. 33,875
Agent for Applicant